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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/850,258	05/07/2001	Patricia M. Rodier	176/60183 (6-11407-674)	1548

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EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/850,258	RODIER ET AL.	
	Examiner	Art Unit	
	Jehanne Souaya Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

S.M.

Status

1)☒ Responsive to communication(s) filed on *03 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37,41 and 43-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37,41,43,45 and 47* is/are rejected.

7)☒ Claim(s) *44 and 46* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Currently, claims 37, 41, and newly added claims 43-47 are pending in the instant application. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. The following rejections are newly applied necessitated by amendment. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is FINAL.

2. The amendments to claims 37 and 41 have obviated the rejection made under 35 USC 102(b), over Accession number A30242, in the previous office action.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

Written Description

4. Claims 37, 41, 43, 45, and 47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 37 encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO: 2 with a single amino acid substitution at position 73. Claim 43 encompasses a polypeptide

comprising the amino acid sequence of SEQ ID NO: 2 with a basic side chain amino acid substitution at position 73. Such claims encompass a large genus of polypeptides and fragments including possible functional and non functional mutants of SEQ ID NO: 2. The specification has taught a single mutant, wherein position 73 of SEQ ID NO: 2 is substituted with Arginine (SEQ ID NO: 4). The specification has taught an association between patients who have this mutated polypeptide and autism. However, the specification has not taught how this mutations affects Hox A1 function, whether it enhances, diminishes, or abolishes Hox A1 function, or how such alteration in function is associated with autism. As such, the specification has not taught a representative number of mutant polypeptides associated with autism.

Claim 41 encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO: 6 with any 3 amino acid insertion. Claims 45 and 47 appear to encompass fragments of claims 45 and 47. Such claims encompass a large genus of polypeptides and fragments including possible functional and non functional mutants of SEQ ID NO: 6. The specification has taught a single mutant, wherein a His-Ser-Ala peptide is inserted between positions 27 and 28 of SEQ ID NO: 6 (SEQ ID NO: 8). The specification has taught an association between patients who have this mutated polypeptide and autism. However, the specification has not taught how this mutations affects Hox B1 function, whether it enhances, diminishes, or abolishes Hox B1 function, or how such alteration in function is associated with autism. As such, the specification has not taught a representative number of mutant polypeptides associated with autism.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry,

whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of SEQ ID NOS: 4 and 8, the skilled artisan cannot envision the detailed chemical structure of the encompassed proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

The response traverses the rejection. The response asserts that Claim 37 recites an isolated peptide with a substitution at position 73, for histidine which encompasses a genus of 19

amino acid species. The response further asserts that it is well known that a single mutation can alter the protein folding and thereby alter functionality which is particularly true when the amino acid varies with respect to charge and polarity. Therefore, the response concludes that since the His to Arg marker for autism a substitution of one positive charged polar amino acid for another, a skilled practitioner would recognize that the substitution of other amino acids at position 73 would alter HoxA1 function and thereby constitute a marker for autism, and that the Arg substitution represents the genus of Hox A1 polymorphisms. This argument has been thoroughly reviewed but was not found persuasive. In the instant case, the specification has not taught or described how the His-Arg substitution affects function of Hox A1 or how this substitution is associated with autism. As such, the specification has not taught a correlation between the structure of the mutant polypeptide and HoxA1 function or lack thereof, or how the mutant polypeptide functions or does not function with respect to autism. The specification does not teach whether Hox A1 function is decreased, enhanced, or abolished. It is therefore unclear whether any other amino acid, including another polar, basic amino acid, would result in the same alteration. Since both His and Arg are polar basic amino acids, and an association with autism is found with regard to the mutant and not the wildtype polypeptide, it is unclear how the substitution of a polar basic side chain alters, diminishes, enhances, or abolishes HoxA1 function, the substitution of an Arg at position 73 is not representative of polar basic amino acids because His, the wildtype amino acid at position 73, does not show any association with autism. Further, since the specification does not teach or describe wildtype or mutant HoxA1 function, how a substitution at position 73 would enhance, alter, diminish or abolish Hox A1 function, or how such would be associated with autism, the substitution of an Arg at position 73 is not

representative of the large genus of the remaining 17 amino acids because. While the mutation to an arginine at position 73 of SEQ ID NO 2 appears to be a marker for autism, the specification does not teach how the structure of this mutant polypeptide functions in such an association.

The response asserts that claim 41 recites an isolated polypeptide with an insertion of 3 amino acids between positions 27 and 28 of SEQ ID NO: 6. The response asserts that the specification teaches of an insertion of His-Ser-Ala which is a marker for autism. The response asserts that although the genus of possible insertions is large, it is commonly known in the art of molecular biology that missense mutations generally alter protein functions and therefore a skilled practitioner would recognize that insertion of other 3 amino acid combinations would also alter HoxB1 function. This argument was thoroughly reviewed but was not found persuasive. In the instant case, the specification has not taught or described how the His-Ser-Ala substitution affects function of Hox B1 or how this substitution is associated with autism. As such, the specification has not taught a correlation between the structure of the mutant polypeptide and HoxB1 function or lack thereof, or how the mutant polypeptide functions or does not function with respect to autism. The specification does not teach whether Hox B1 function is decreased, enhanced, or abolished. It is therefore unclear whether any other amino acid insertion would result in the same alteration or association. It should be noted that there are 8000 different permutations of possible 3 amino acid inserts. Since the specification has not taught or described how the structure of the His-Ser-Ala insertion affects HoxB1 function or how it affects HoxB1 such that the mutant is associated with autism, the disclosure of the His-Ser-Ala insertion is not representative of the extremely large genus of possible mutant polypeptides encompassed by the claims.

Indefinite

5. Claims 45 and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "fragment comprises" in claims 45 and 47 is confusing as it is unclear if the claimed peptide is a fragment only from within the polypeptides of claims 37 or 41, with no undisclosed amino acid sequences on either side (but with the corresponding substitution or insertion) or whether the claims are drawn to a polypeptide which need only minimally "comprise" an amino acid substitution corresponding to position 73 of SEQ ID NO: 2, or any 3 amino acid insertion.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claim 45 is rejected under 35 U.S.C. 102(a) as being anticipated by Chen et al (hereinafter referred to as Chen, J. Agric. Food Chem, vol 44, pages 2619-2623; 1996).

Claim 45 encompasses a fragment of SEQ ID NO: 2 which includes position 73 of SEQ ID NO: 2, wherein the histidine at position 73 is substituted with any amino acid. Such a fragment includes any 4 mer peptide corresponding to positions 72-75 (HHHP) of SEQ ID NO: 2, where the second H (corresponding to position 73 of SEQ ID NO 2) is any amino acid. Chen

teaches the polypeptide HLHP (see Figure 4 and table 1). The teachings of Chen therefore anticipate the instant claim.

8. Claim 47 is rejected under 35 U.S.C. 102(b) as being anticipated by Kohmura et al (hereinafter referred to as Kohmura, Agric. Biol. Chem. Vol 53, pages 2107-2114, 1989).

Claim 47 encompasses a fragment of SEQ ID NO: 6 which includes a 3 amino acid insertion between positions 27 and 28 of SEQ ID NO: 6. Such a fragment includes, for example, any 4 mer peptide that includes any 3 amino acid insertion. For example, a 4 mer peptide included by the broad scope of the claims would be any peptide with Ala-Xaa-Xaa-Xaa (Xaa being any amino acid, Ala corresponding to position 27 of SEQ ID NO: 6) or Xaa-Xaa-Xaa-Pro (Xaa being any amino acid, Pro corresponding to position 28 of SEQ ID NO: 6). Kohmura teaches the peptides ALPP, LPLP, EVLP, VPQP, and LLNP (see table 1), any of which anticipate the instant claim.

9. Claims 45 and 47 are rejected under 35 U.S.C. 102(b) as being anticipated by accession number A30242 (December 1989).

The claims are broadly drawn to a polypeptide fragment comprising a single amino acid substitution at position 73 of SEQ ID NO: 2 (claim 45) or a polypeptide fragment comprising a 3 amino acid insertion between positions 27 and 28 of SEQ ID NO: 6 (claim 47). The claims have been broadly interpreted to encompass a polypeptide comprising a single amino acid substitution at position 73 of SEQ ID NO: 2 or a polypeptide comprising 3 amino acid insertion between positions 27 and 28 of SEQ ID NO: 6. The recitation of fragment in the claims does not limit the length of polypeptides encompassed by the claims. Further the claims do not specify how much of the corresponding SEQ ID NOS are needed in the fragments. Therefore, the claims have been

broadly interpreted to encompass the polypeptide taught by Accession number A30242. Accession number A30242 teaches a polypeptide (inherently encoded by a nucleic acid) which contains an arginine (one of the possible single base substitution at position 73 of SEQ ID NO: 2). With regard to claim 47, as no specific amino acid sequence is presented, the insertion could be any amino acid sequence. Therefore, accession number A30242 anticipates claim 47 as well.

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Claims 44 and 46 are objected to for being dependent on rejected claims. Such claims would be allowed if written in independent form.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-

0572. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

Note: The examiner's name has changed from Jehanne Souaya to Jehanne Sitton. All future correspondence to the examiner should reflect the change in name.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (571) 272-0507.

Jehanne Sitton

Jehanne (Souaya) Sitton
Primary Examiner
Art Unit 1634
2/19/04

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